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THE PREVALENCE OF CARDIOVASCULAR RISKS IN HIV-INFECTED PERSONS IN CARE IN CROATIA IN 2015

Graduate Thesis

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This graduate thesis was made at the University of Zagreb, School of Medicine at the department of Infectious Diseases, division HIV/AIDS, University Hospital Zagreb, mentored by Professor Josip Begovac, M.D., PhD, and was submitted for evaluation in 2016.

List of abbreviations:

ACC/AHA–American College of Cardiology/American Heart Association

AIDS–Acquired immunodeficiency syndrome

ASCVD–Pooled Cohort Atheroslcerotic CVD risk equations

CART–Combination antiretroviral therapy

CHD–Coronary heart disease

CVD–Cardiovascular disease

DAD–Data collection on adverse events of anti-HIV drugs

EACS–European Aids Clinical Society Guidelines

ESC/EAS–European Society of Cardiology/European Atherosclerosis Society

FRS–The Framingham risk score

ART–Antiretroviral therapy

HDL–high-density lipoprotein (cholesterol)

HIV–Human immunodeficiency virus

IMT–Intima-media thickness

InSTI– Integrase strand transfer inhibitors

LDL–Low-density lipoprotein (cholesterol)

NNRTI–Non nucleos(t)ide reverse transcriptase inhibitor

NRTI–Nucleos(t)ide reverse transcriptase inhibitor

PI–Protease inhibitor

SCORE–European Systematic Coronary Risk Evaluation Score

TC–Total cholesterol

TG–Triglycerides

VLDL–Very low-density lipoprotein cholesterol

UHID – University Hospital for Infectious Diseases

Contents:

Summary:

Title: “THE PREVALENCE OF CARDIOVASCULAR RISKS IN HIV-INFECTED PERSONS IN CARE IN CROATIA IN 2015.”

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Abstract:

Aim:This review will aim at considering the prevalence of cardiovascular risks among the HIV-infected population undergoing ART therapy in Croatia: Cardiovascular diseases are now among the most common causes of mortality in people living with HIV. We will see for which reasons people living with HIV appear to have an elevated risk for cardiovascular diseases.

Method: A cross-sectional analysis of 310 consecutive HIV infected patients seen during a routine clinical visit aged 40 to 79 years was performed in Zagreb from June 2014 to March 2016. All the next cardiovascular risks factors were systematically assessed: age, gender, race, total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, smoking, diabetes(blood glucose measurements), treated for high blood pressure (yes or no), past and current history of ART (particularly, duration of treatment including abacavir, indinavir and lopinavir (DAD)). Were also systematically collected CD4+ cell count, HIV viral load, family history of premature CVD, past medical history of CVD.

Results: Among the 310 persons included into the study, 42% were current smokers, 23% were hypertensive, 34% had Hypercholesterolemia (>6.2 mmol/L), 38% of patients were overweight, 12% were obese, 27% exhibited metabolic syndrome, 7.8% of patients had past cardiovascular event, 12.9% patients had a family history of premature cardiovascular event, 21% of patients were already treated for high blood pressure, 18.4% were already treated with lipid-lowering agents, 46% of the studied population had an abacavir-including antiretroviral regimen, 10% of patients had a detectable viral load, and 11.6% of patients had a low CD4+ cell count (<350 per mm3).

Conclusion : : Among the HIV-infected persons in care in Croatia in 2015, the prevalence of a compound collection of major cardiovascular risk factors is high.

Key words: ART dyslipidemia prevalence cardiovascular risk Croatia

INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) combinations for human immunodeficiency virus (HIV)-infected patients, which was for the first time able to effectively suppress the replication of HIV and dramatically reduce both mortality and morbidity, has resulted in a better and longer quality of life for HIV-patients [1]. These innovative combinations have dramatically changed their life's perspectives [2].

The different ART combinations, all composed of at least three different antiretroviral drugs, can manage to reduce viral load to undetectable levels [3]. ART combinations prevent viral replication by acting at different stages of the viral replication cycle [4]. They are classified in different therapeutic groups according to their action's mechanism: integrase strand transfer inhibitors (InSTIs) [5], entry inhibitors [CC chemokine receptor-5 antagonists][6], fusion inhibitors [7], protease inhibitors (PIs)[8], nonnucleoside reverse transcriptase inhibitors (NNRTIs)[9] and nucleoside reverse transcriptase inhibitors (NRTIs)[10]. Aside from the substantial benefits on viremia that result from the use of various ART combinations, laboratory and clinical experience has shown that ART can induce severe and considerable adverse effects on metabolic complications of lipid metabolism, characterized by signs of lipodystrophy, insulin resistance, central adiposity, dyslipidemia, increased risk of cardiovascular disease and even an increased risk of atherosclerosis [11-14]. Noteworthily, other individual factors may be involved in the metabolic and lipid alterations observed because not all of the patients exposed to the same ART regimens are similarly affected [15-17]. All of these changes in the aspects of lipid metabolism during HIV infection, specifically changes in high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL), triglycerides (TG), lipid peroxidation, and their relationship with atherosclerosis in HIV-infected patients, are a result of the critical role of cholesterol in the mechanism of HIV replication [13,14,18,19]. HIV decreases plasma HDL by impairing the cholesterol-dependent efflux transporter ATP-binding cassette protein A1 in human macrophages, which is a condition that has a high atherogenic risk [20,21].

ART-associated lipid disorders:

Cardiovascular risk associated to PIs regimens

The use of PI-based ART constitutes a strong option against HIV infection because it prevents both the maturation of viral particles and controls the infection of new cells by HIV. Unfortunately this virological efficiency often goes along with changes in lipid metabolism in HIV patients and dyslipidemias have been associated with this class of antiretroviral drugs [11,12,22,23]. PIs are associated with increased hepatic triglycerides-synthesis, VLDL, and to a lesser extent, total cholesterol (TC) [11-14]. It has also been observed that these drugs impair the hydrolysis of triglyceride-rich lipoproteins by lipase, which reduces the storage of free fatty acids and interferes with the normal postprandial metabolism of free fatty acids [22,24]. The PIs are analogous substrates of the aspartyl protease enzyme of HIV that are involved in the cleavage process of viral proteins and form smaller functional viral particles with infective capacity. After the cleavage process, the newly formed infectious viral particles are released from infected cells in a mature form [8,25,26]. Once the PIs bind to the active site of the protease enzyme, and this process of cleavage is blocked, there is interference in the enzyme activity and inhibition in the process of viral maturation and the formation of infectious viral particles [25,26]. The different mechanisms by which PIs promote these changes remain unknown. However, the main effect of PIs seems to be suppressing the breakdown of the nuclear form of sterol-regulatory element binding protein-1 in the liver and adipose tissue. This regulator is a key element in the proteolytic pathway responsible for regulating cellular and plasma levels of fat and cholesterol [27].

Of course, other classes of antiretroviral drugs are available, including those with excellent activity against viral replication without having any apparent effect on lipid metabolism [13,22,28]; but it is clear that the use and recommendation of PIs occurs in situations where other drugs have not achieved the targeted effect, either by nonadherence to treatment, viral resistance or lack of an immune response [29,30]. Moreover, once the therapy with PIs is initiated, a change to a more conservative therapy without their use is not recommended nor used in clinical practice [31,32].

Thus, a continuous search that considers the individual characteristics of each PI available as a current therapy is needed to achieve alternative ARTregimens that can maintain a suppression of viremia with minor effects on the lipid metabolism of HIV patients [31,33].

Cardiovascular risk associated to NRTIs

Evaluation of the potential contribution of nucleos(t)ide reverse transcriptase inhibitors (NRTI) on the increased cardiovascular risk in HIV patients on ART within the D:A:D study revealed an increased risk for myocardial infarction in patients being treated with abacavir or exposed to this drug within the preceding 6 months was reported for the first time [34]. These findings were confirmed by several studies, but not all: A french study based on Hospital database short-term/recent exposure to abacavir was associated with an increased risk of myocardial infarction in the overall cohort [odds ratio (OR) 2.01; 95% confidence interval (CI), 1.11–3.64] but not in the subset of matched cases and controls who did not use cocaine or intravenous drugs (OR:1.27; CI: 0.64–2.49). This has raised the question as to how far cohort studies can adjust for all potential confounding factors which may contribute to cardiovascular risk and which may have been over-represented in the abacavir-treated patients.

With regard to other NRTIs no increased risk has been found. Table 1 summarizes the main classes of antiretroviral drugs, their effects on lipid and glucose metabolism, and the potential for contributing to the risk of CVD. Azidothymidine, a NRTI and component of first line ART, has been described to cause cardiac dysfunction induced by mitochondrial toxicity [35,36] in two reports on adults, where three larger studies could not confirm any association between exposure to azidothymidine and myocardial dysfunction [37-39]…

Cardiovascular risk associated to NNRTIs

If Protease inhibitors (PIs) are recognized as having the greatest impact in terms of metabolic complications, followed by nucleoside reverse transcriptase inhibitors, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) have the least impact [40] and appear to be among the most neutral regarding metabolic changes (dyslipidemias and glucose regulation impairment). In particular, regimens based on the NNRTI nevirapine have been shown to achieve significant metabolic benefits and may help to improve dyslipidemias.

Drug Class	Generic name	Effects on lipids	Effects on glucose	Impact on coronary artery disease
Nucleos(t)ide Reverse Transcriptase Inhibitors: (NRTI)	Abacavir(ABC) Azidothymidine Didanozine(ddI) Emtricitabine(FTC) Lamivudine(3TC) Stavudine(d4T) Tenofovir(TDF)	TC↑ LDL↑ TC↑ LDL↑ Dyslipidemia++ Neutral Neutral Dyslipidemia + TC↓ LDL↓	No effect Insulin resistance+ Insulin resistance+ No effect No effect Insulin resistance+ No effect	Increased risk of MI (controversial) No association No association No association No association No association No association
Non-Nucleoside Reverse Transcriptase Inhibitors : (NNRTI)	Efavirenz(EFV) Etravirine(ETR) Nevirapine(NVP) Rilpivirine(RPV)	TC↑ LDL↑ Neutral HDL↑ Neutral	No effect --- --- ---	No association --- No association ---
Protease Inhibitors: (PI)	Ritonavir Amprenavir+ Ritonavir Fosamprenavir+Ritonavir Atazanavir+ Ritonavir Darunavir+ Ritonavir Indinavir Lopinavir+Ritonavir Nelfinavir Saquinavir Tipranavir+ Ritonavir	**Dyslipidaemia +++** **Dyslipidaemia ++** **Dyslipidaemia ++** Dyslipidaemia + Dyslipidaemia + Dyslipidaemia + **Dyslipidaemia+++** Dyslipidaemia + Dyslipidaemia + Dyslipidaemia +	**Insulin resistance +++** Insulin resistance + Insulin resistance + Insulin resistance + Insulin resistance + **Insulin resistance +++** **Insulin resistance +++** Insulin resistance + Insulin resistance + Insulin resistance +	Cumulative exposure increases risk for MI Cumulative exposure increases risk for MI Cumulative exposure increases risk for MI No association --- Controversial results Cumulative exposure increases risk for MI No association No association ---
Integrase strand transfer inhibitors: (InSTI)	Elvitregravir+ Cobicistat Raltegravir Dolutegravir	Neutral Neutral Neutral	No effect No effect No effect	No association No association No association
Entry inhibitors: (CC chemokine receptor 5 antagonists)	Maraviroc Enfuvirtide	Neutral Neutral	No effect No effect	--- ---

Table1: Main Classes of antiretroviral drugs and their impact on lipid and glucose metabolism and coronary artery disease. Dyslipidemia is defined by increased TC, LDL, TG and decreased HDL. MI, myocardial infarction. [41]

Impact of diabetes on cardiovascular disease in human immunodeficiency virus

Among the developped countries,an increasing proportion of the population is or will have to deal with diabetes mellitus: This growing civilization's disease turns to be a major public health issue and CVD is the leading cause of morbidity and mortality among diabetic patients [42].

For HIV patients, age, BMI and sex remain the major risk factors for diabetes mellitus [43]. No studies have been able to link HIV infection itself (in ART-naive patients) with diabetes mellitus, suggesting no increased risk of diabetes mellitus by HIV infection [44]; but increased rates of insulin resistance have been observed in ART-naive HIV patients. The risk of diabetes in HIV is enhanced once patients start on ART [43–45]. We already mentionned adverse effects Protease inhibitors over lipids metabolism, but they also reversibly increase insulin resistance,the risk of diabetes and subsequently the risk for CVD through the inhibition of glucose translocation through GLUT4 [46].

The NRTIs azidothymidine and stavudine appear to have a direct effect on glucose metabolism through mitochondrial toxicity [47,48].

A French systematic hospital database nationwide review has shown that the increased long-term risk for heart failure in HIV-infected compared with HIV-negative patients was independently associated with HIV +/- diabetes at 12-month follow-up [49]. These results advocate for the crutial importance of glucose monitoring in patients on ART, especially in patients on PIs and older NRTIs.

The prevalence of cardiovascular risks in HIV-infected patients in care in Croatia in 2015

The specific datas concerning Croatia are arising from a cross-sectional study performed at the university hospital for infectious diseases “Fran Mihaljevic” Zagreb by Doctors

Vanja Romih Pintar and Pr.Dr Josip Begovac. Due to the fact that Croatia has a centralized system of treatment and care of persons infected with HIV, the datas collected there are therefore national.

Objective: This analysis aimed at assessing and specifying the prevalence of cardiovascular risks factors among the HIV-infected population at the UHID Zagreb.

Method: Over a period starting from June 2th 2014 to March 14th 2016, 310 consecutive HIV infected patients have been examined during a routine clinical follow-up visit . They were aged 40 to 79 years and were retracted from the study in case of acute illness or exacerbation of chronic illness at the time of theevaluation. Pregnant women were also excluded. All the next cardiovascular risks factors were systematically assessed: age, gender, race, total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, smoking, diabetes(blood glucose measurements), treated for high blood pressure (yes or no), past and current history of ART (particularly, duration of treatment including abacavir, indinavir and lopinavir (DAD)). Were also collected CD4+ cell count, HIV viral load, family history of premature CVD, past medical history of CVD.

Relying on the datas collected during this cross-sectional study, have been compared four cardiovascular disease risk models: The Framingham risk score (FRS), the Pooled Cohort Atheroslcerotic CVD risk equations (ASCVD), the European Systematic Coronary Risk Evaluation Score (SCORE) and the Data Colletion on Adverse Effects of Anti-HIV Drug study (DAD). Patients have been categorized according to these four CVD risks models in "high cardiovascular risk patients" and "non high cardiovascular risk patients". High risk: FRS-10y> 20%; SCORE-10y > 5%; ASCVD-10y > 7,5%; DAD -5y> 5%.

Definitions

CVD was considered present if a history of any of the following conditions existed on inclusion into the study: myocardial infarction, stable/unstable angina, invasive coronary artery procedure, carotid artery disease (symptomatic like transient ischemic attack or stroke, or >50 percent stenosis on angiography or ultrasound), stroke, peripheral artery disease, abdominal aortic aneurysm or other forms of clinical atherosclerotic disease (eg, renal artery disease).

Family history of premature cardiovascular events was considered present if the event occurred in a male first-degree relative <55 years or female first degree relative <65 years.

Diabetes mellitus was defined if at least two fasting plasma glucose levels were ≥7.0 mmol/L, casual plasma glucose >11.1 mmol/L, or if patient had a history of diabetes treatment.

Arterial hypertension was defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg (>135/85 mm Hg in diabetic patients) or taking antihypertensive drugs.

Blood pressure was measured by the attending nurse using mercury sphygmomanometers. The patient was in a seated position; his or her arm was supported and flexed at the level of the heart. The stethoscope's bell was lightly pressed over the brachial artery just below the cuff's edge. The first knocking sound (Korotkoff) indicated the patient's systolic pressure and the disappearance of the knocking sound indicated diastolic pressure.

Dyslipidemia was considered present if total cholesterol >6.2 mmol/L, HDL-cholesterol <1.03, or fasting triglycerides >2.26 mmol/L. The modified updated National Cholesterol Education Program criteria were used for the definition of metabolic syndrome: triglycerides of at least 1.7 mmol/L, HDL of 1.0 mmol/L or less in men and of 1.3 mmol/L or less in women, hypertension (systolic blood pressure >130 mm Hg or diastolic blood pressure >85 mm Hg), or use of antihypertensive medications and a glucose level at least 5.6 mmol/L or the diagnosis of diabetes.

Body mass index was used as a surrogate for waist circumference.

Results: The global results indicate that the prevalence of major CVD risk factors **is high** in Croatia among the HIV-treated population in 2015. See details of independant risk factors below:

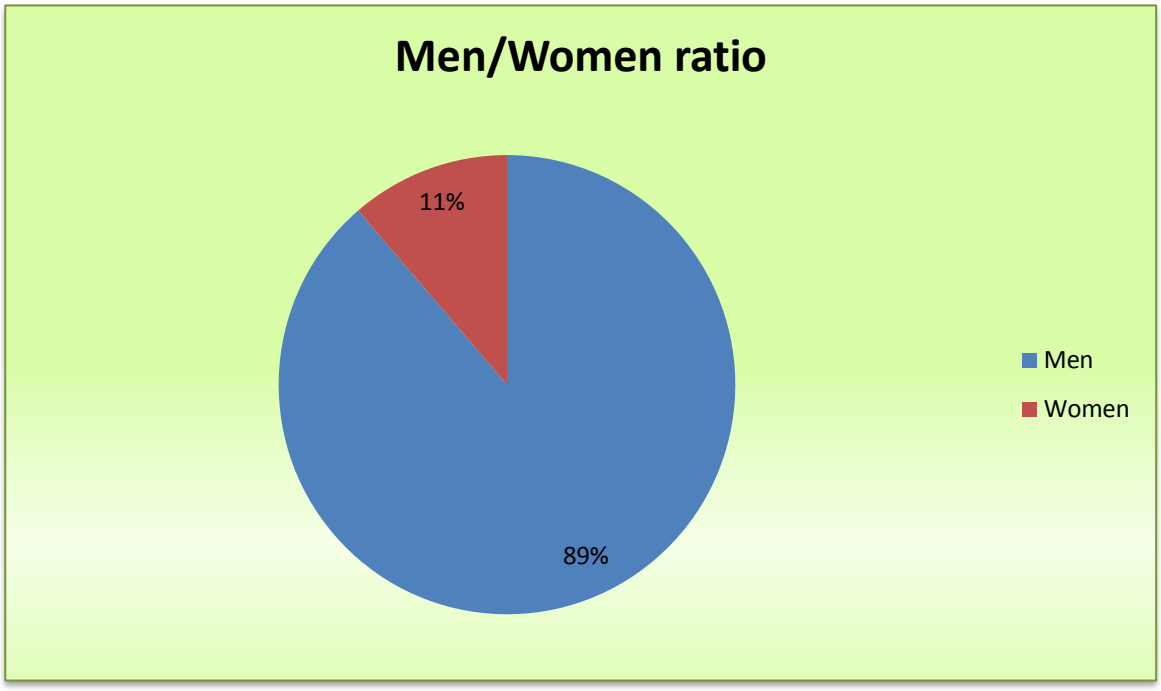


Figure1: Men/Woman ratio.

In the studied population, men are overrepresented compared to the general population, they are **89%**(figure 1). Male sex is a risk factor for cardiovascular diseases.

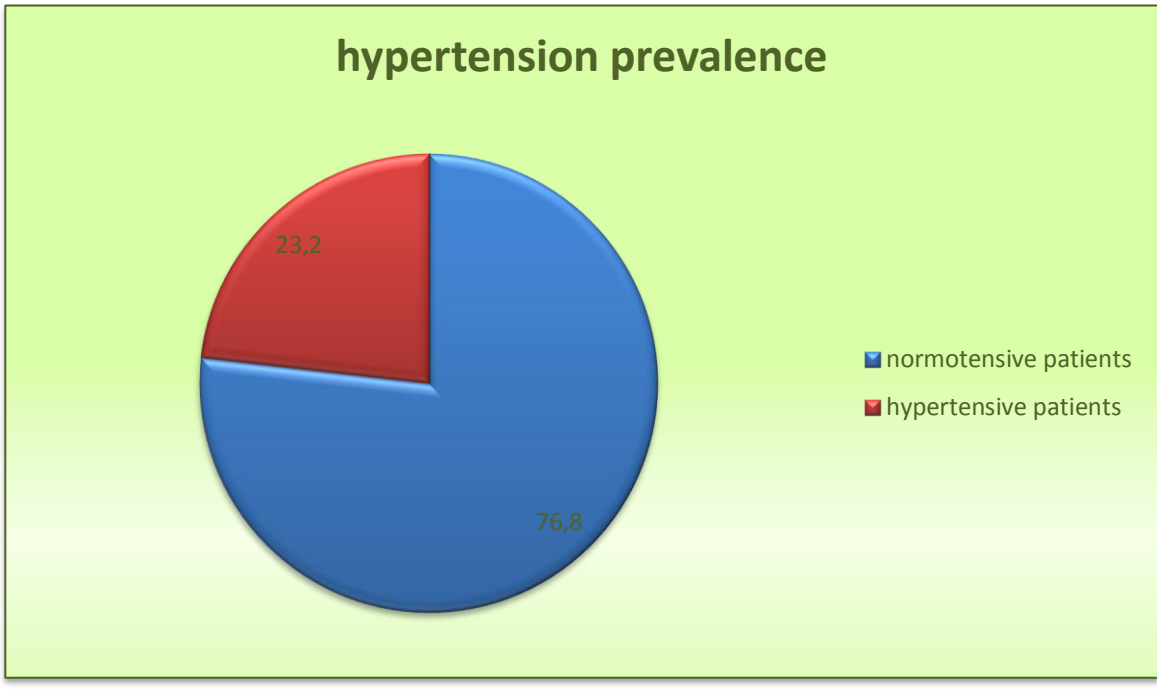


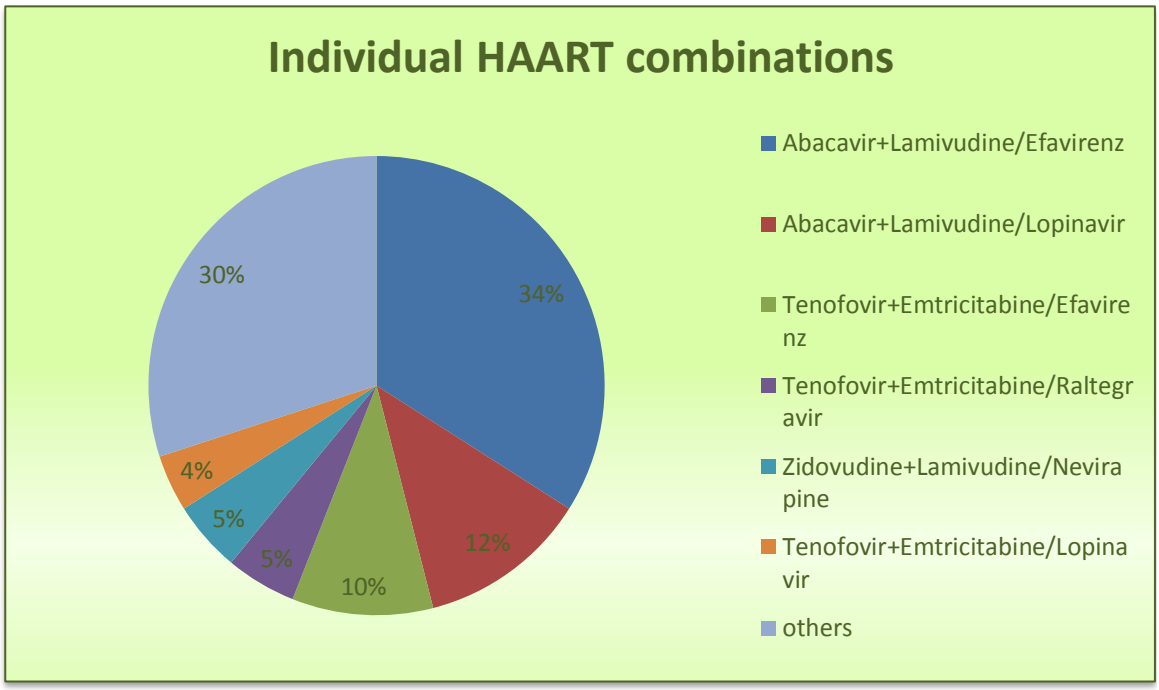
Figure 2: Hypertension prevalence.

Hypertension prevalence is significantly high in the studied population, it reaches **23.2%** (figure 2) According to European guidelines of the European Society of Cardiology and Europen

Atherosclerosis Society (ESC/EAS), hypertension is one if not the main leading independant risk of cardiovascular event (with age).

Individual ART regimens:

Figure 3: individual ART combination.



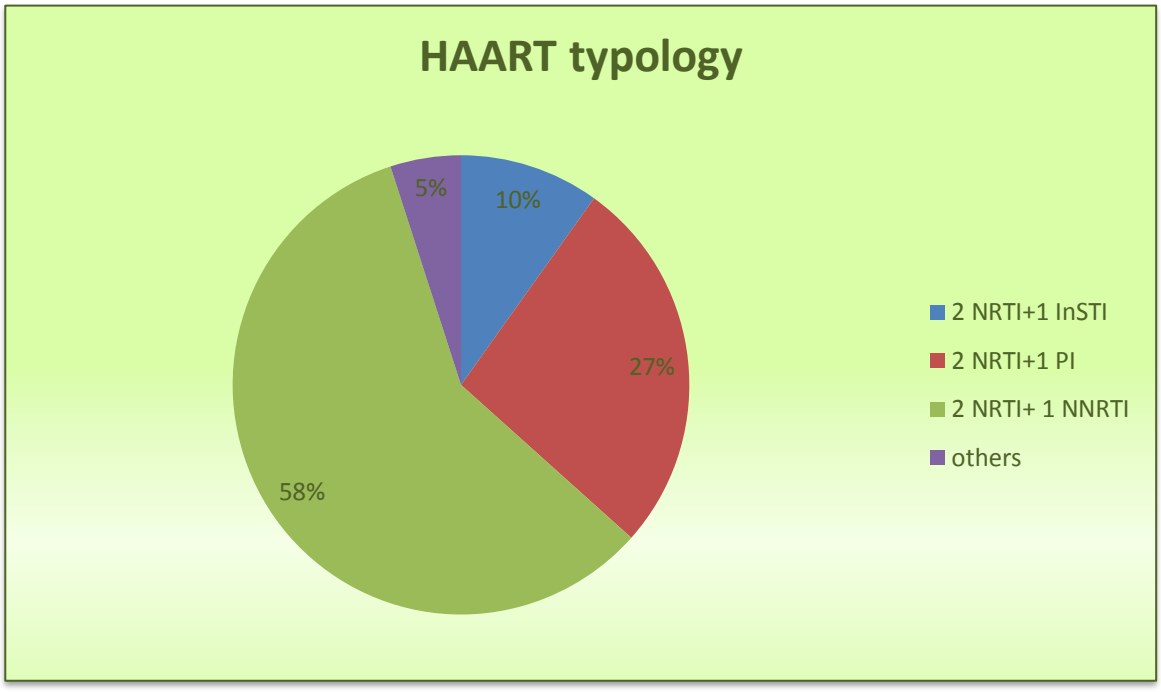


Figure 4: ART Types.

As previously stated, some combinations are more susceptible to induce dyslipideamias and its consequence, atherosclerosis, than others:

- **27%** of patients are having a PI-included ART combination (figure 4).
- Among the 58% of patients treated with 2 NRTI+1NNRTI, only 10% are treated with nevirapine, others are treated with efavirenz which is less favorable regarding the lipids metabolism (figure 3).

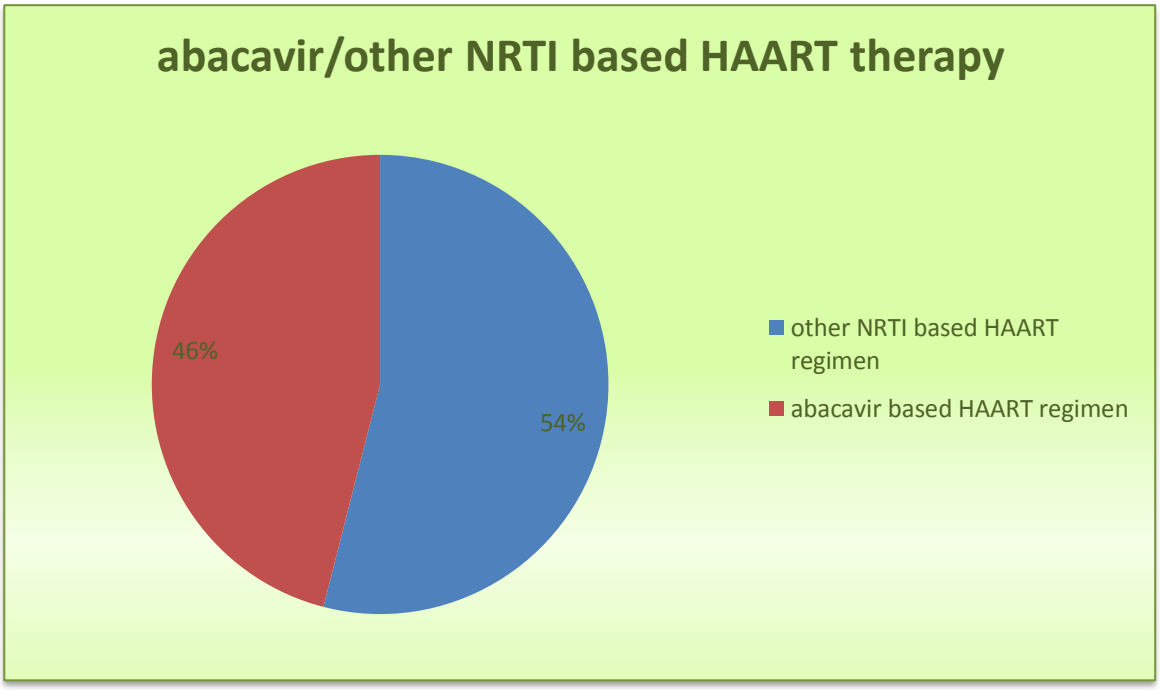


Figure 5: abacavir based-/non abacavir-based regimens.

Abacavir is suspected to be related to an elevated risk of myocardial infarctions[34].

- **46%** of the studied population have an abacavir-including regimen**.**(figure 5)

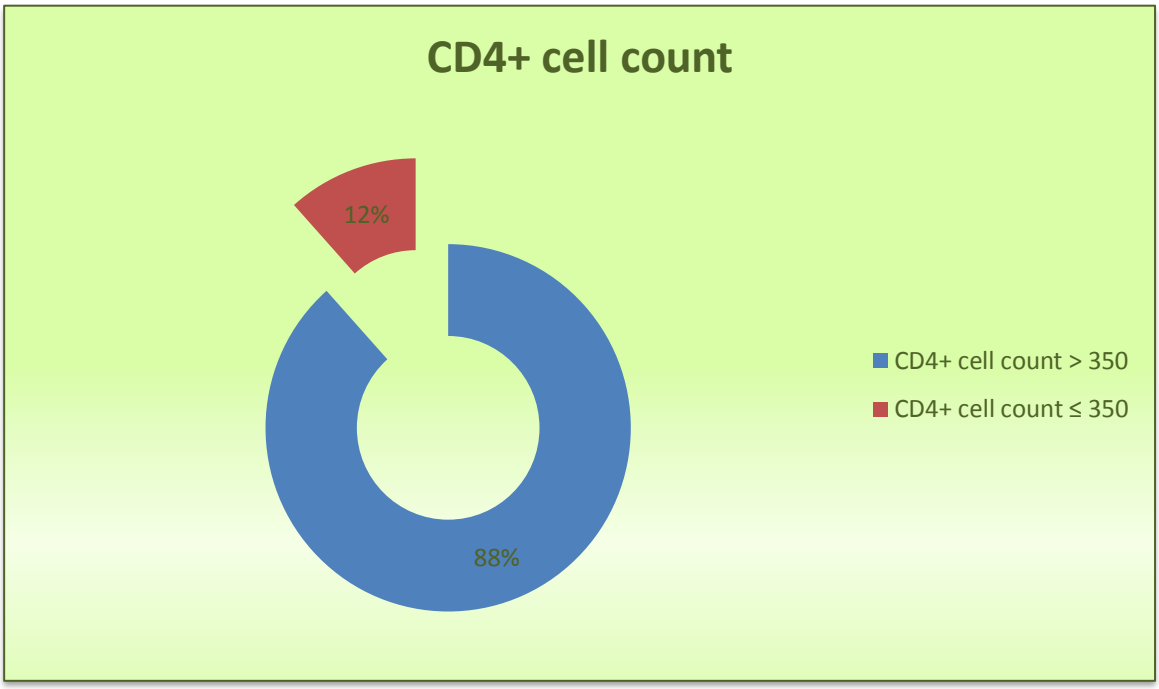


Figure 6: CD4+ cell count.

Low CD4+ T cell count is a risk factor for cardiovascular disease events [50]

In the studied population**, 11.6%** of patients have a low CD4+ cell count (figure 6).

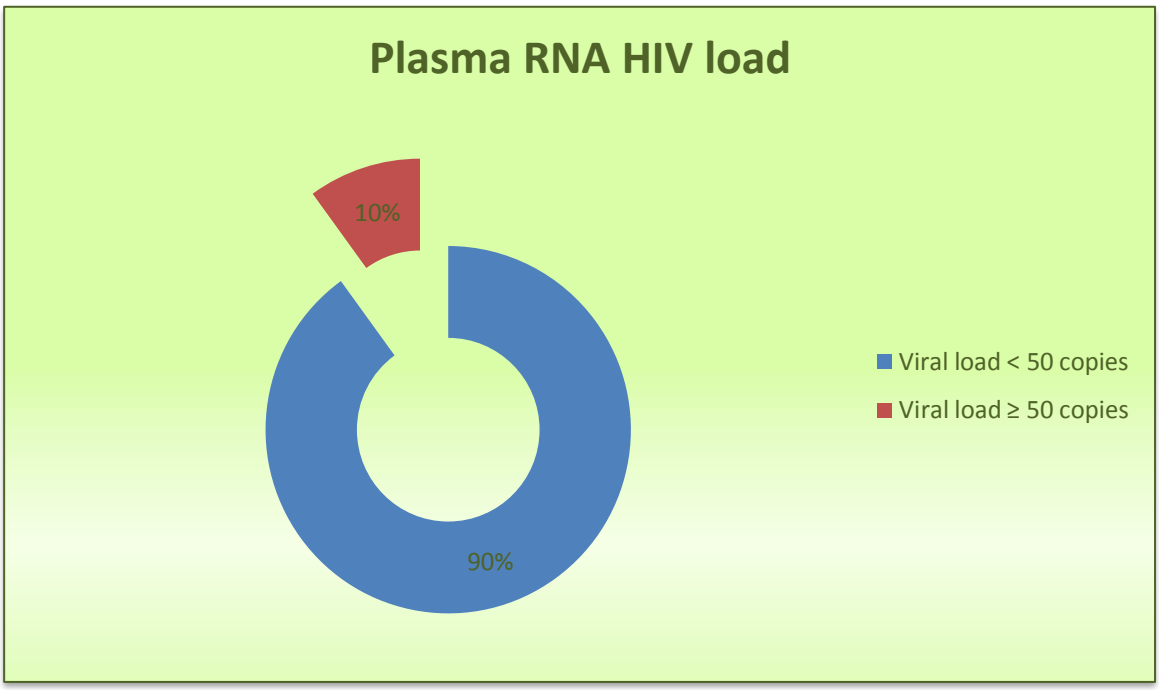


Figure 7: Viral load.

A statistically significant relashionship exists between high HIV RNA load and low HDL-cholesterol [50,51]

- In the studied population**, 10%** of patients have a detectable viral load (figure 7).

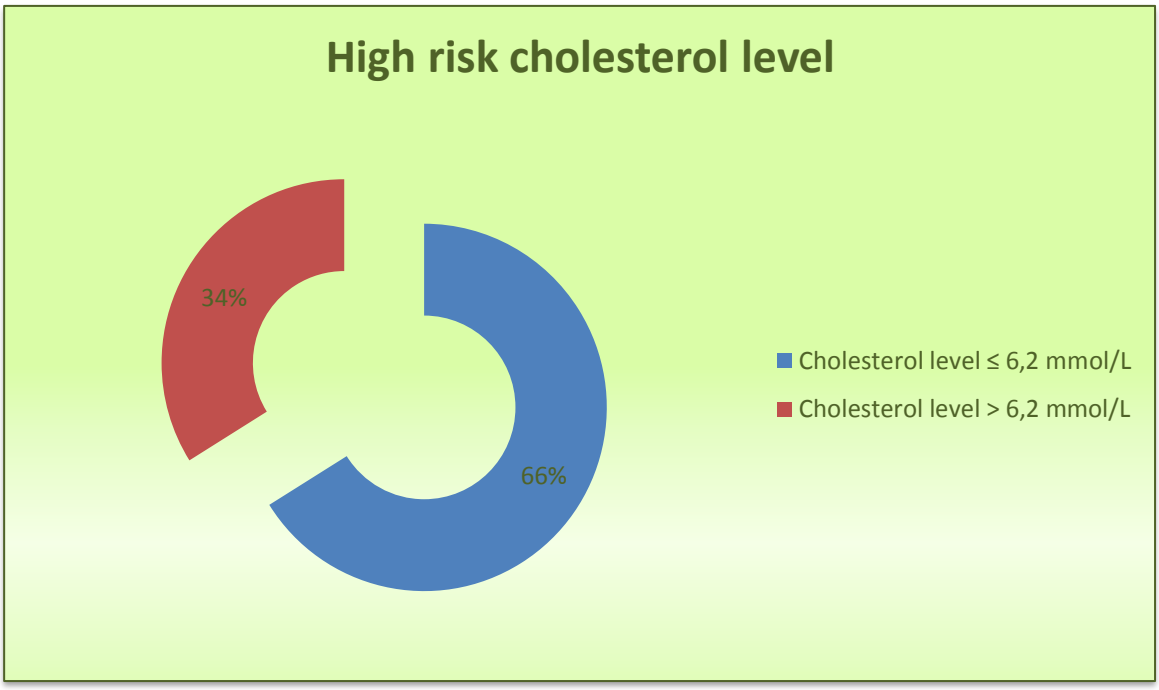


Figure 8: proportion of patients above/below the“high risk“ treshold of 6.2mmol/L of cholesterol (TC)

Cholesterol level above 6.2mmol/L were found in 33.9% of individuals (figure 8).

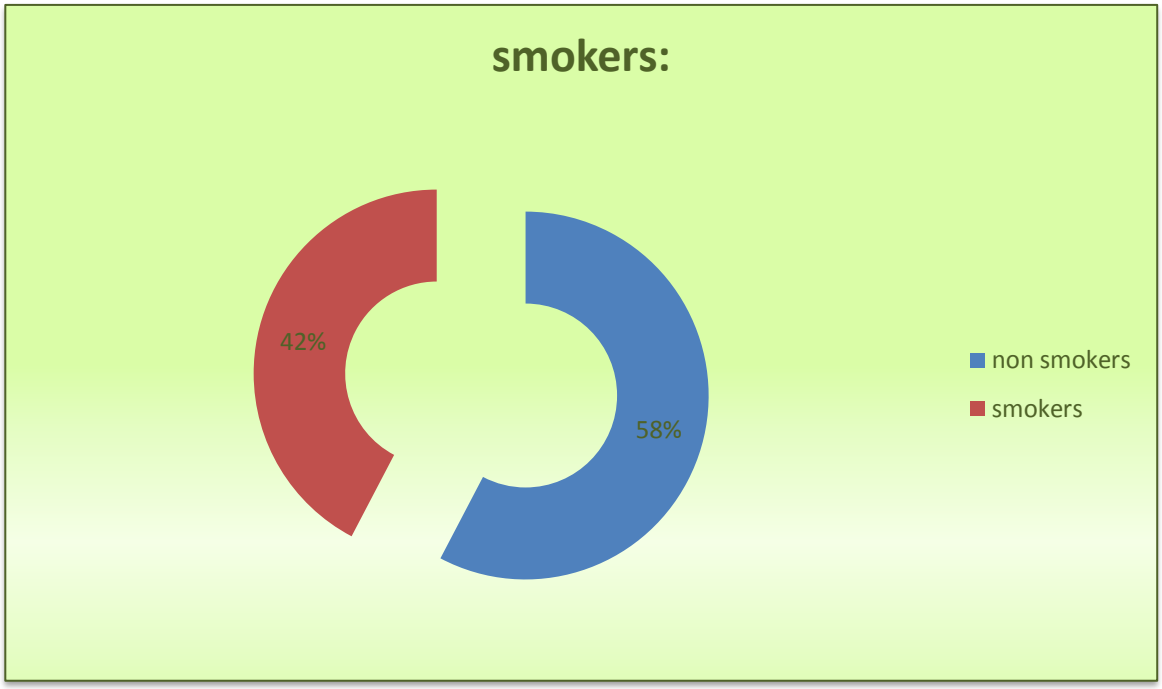


Figure 9: prevalence of smokers.

A very high prevelence of smokers **(42.3%)** is contained in the croatian HIV treated population (figure 9). Not only this population smokes more than the general population, but its body mass index (BMI) repartition is worrisome:

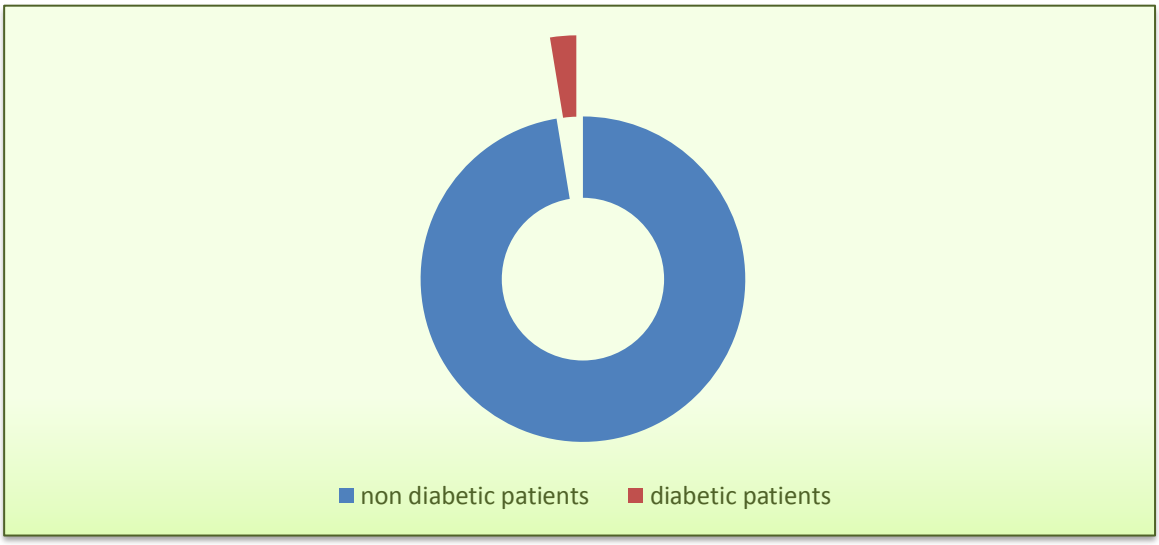


Figure 10: Prevalence of diabetes in HIV-infected population in care:

In the studied population**, 2.6%** of patients exhibit diabetes (figure 10).

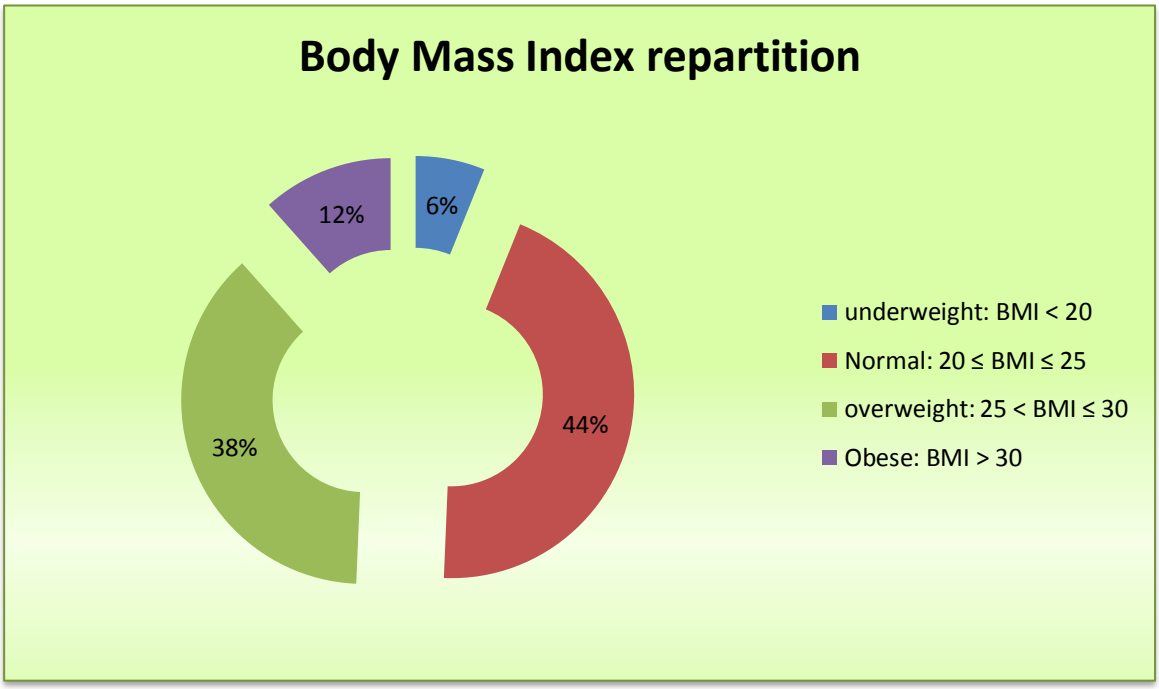


Figure 11: repartition of corpulence.

- In the studied population, **37.7%** of patients are overweight.
- And **11.6%** are obese (figure 11).

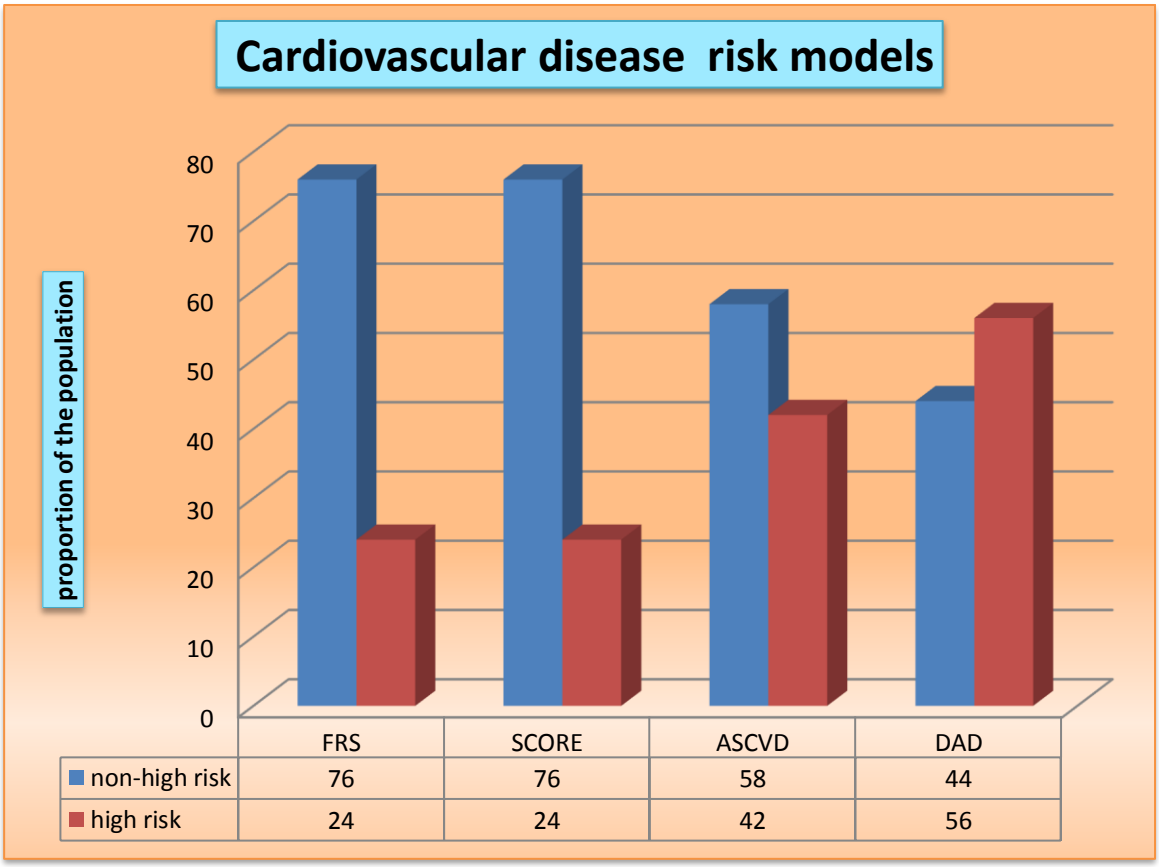


Figure 12: Studied population screened by 4 risk models.The proportion of high and non-high scores are reported.

Even though, the non HIV-specific models are not assessing the CVD risks with a similar range than the DAD does, the global conclusion remains that the prevalence of major CVD risk factors **is high** in Croatia among the HIV-treated (figure 12).

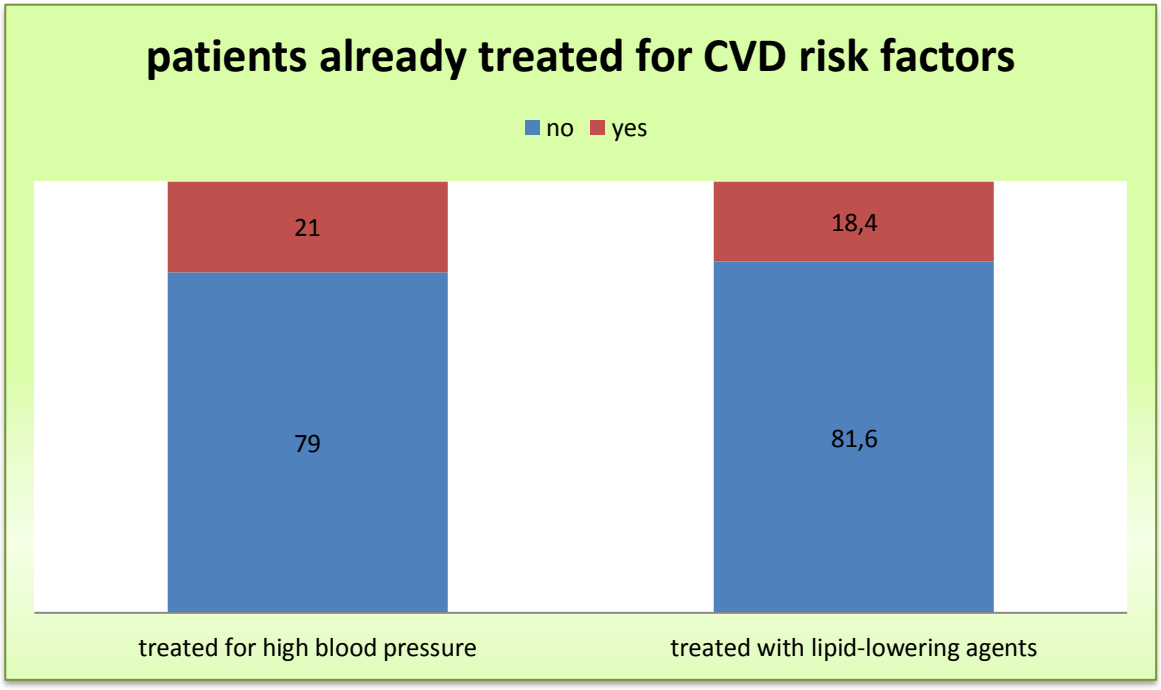


Figure 13:proportion of patients already undergoing treatment against CVD risk factors.

In the studied population, **21%** of patients are already treated for high blood pressure, and **18.4%** are already treated with lipid-lowering agents (figure 13).

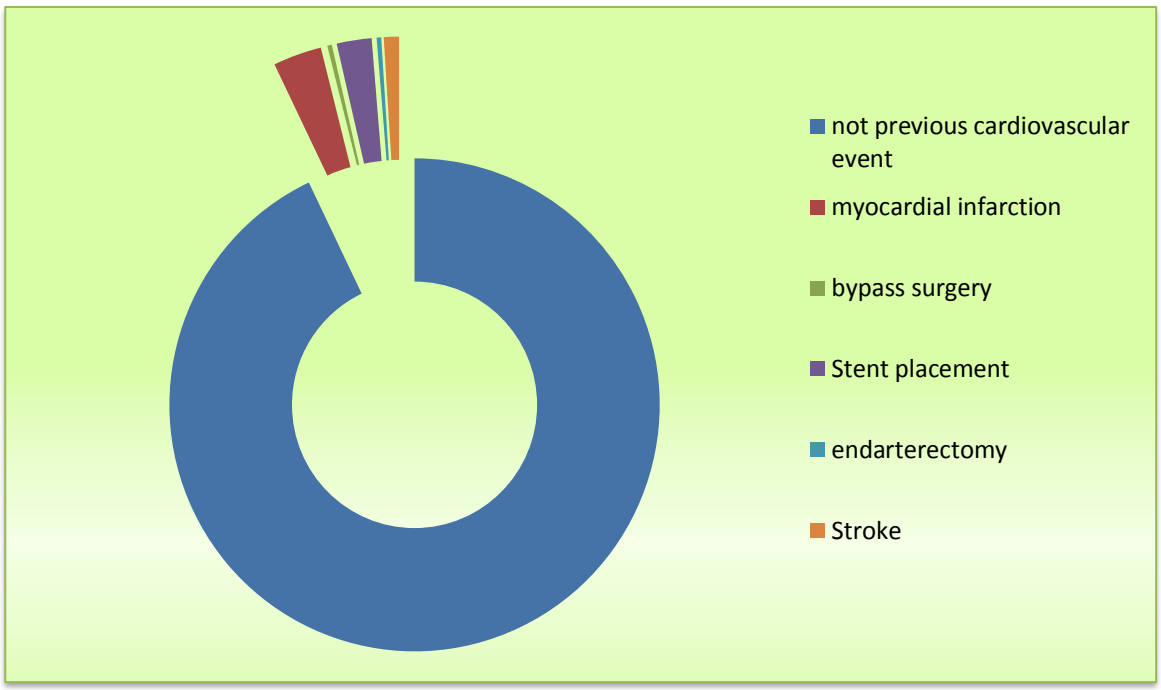


Figure 14: Proportion of patients with past cardiovascular event.

In the studied population, 3.2% of patients suffered previous myocardial infarction, **0.3%** underwent bypass surgery**, 2.3%** stent placement, **1%** endarterectomy and **1%** suffered stroke. In total, **7.8%** of patients had past cardiovascular event (figure 14).

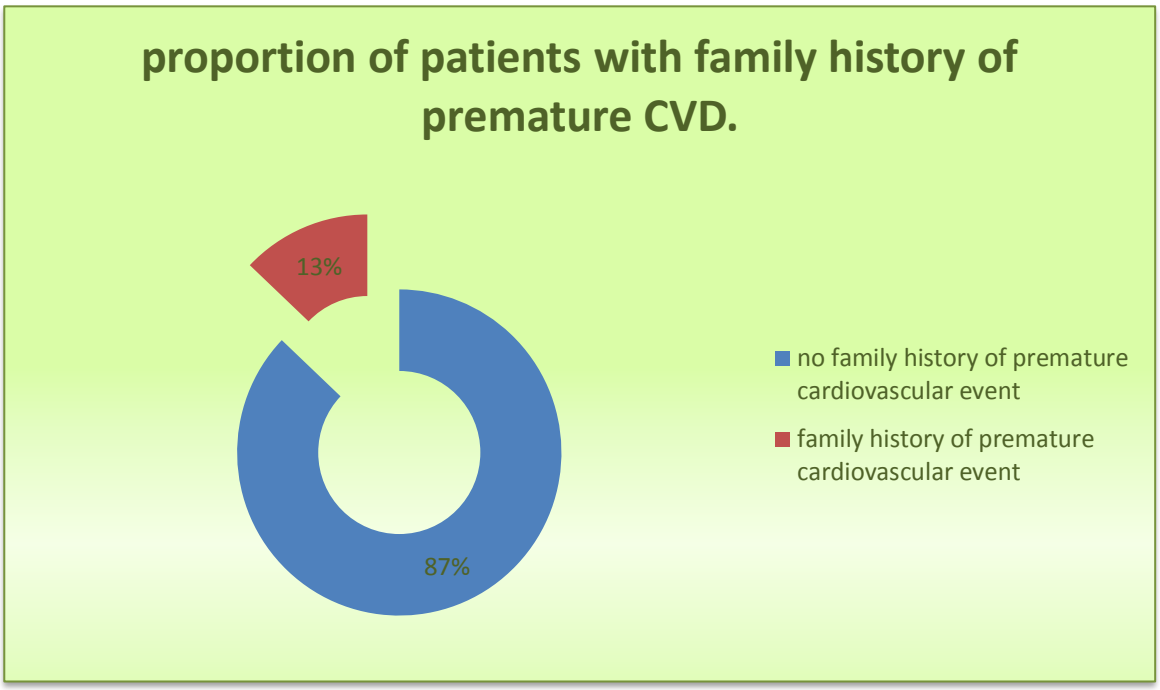


Figure 15: proportion of patients with family history of premature cardiovascular event.

In the studied population, **12.9%** of patients have had a family history of premature cardiovascular event (figure 15).

Discussion

We found a high prevalence of different cardiovascular risk factors in HIV-infected persons in Croatia older than 40 years.

As previously stated, HIV-infected patients have metabolic abnormalities that make them susceptible to atherosclerosis. These abnormalities are caused by the combined effects of HIV infection itself, toxicities of specific antiretroviral therapies, as well as the traditional factors that increase atherosclerotic risk in the non–HIV-infected population: age, gender, smoking , overweight and obesity (Body mass index), systolic and diastolic blood pressure (hypertensive patients), previous cardiovascular event (the patient is then in secondary or tertiary prevention) total cholesterol, HDL-cholesterol and diabetes mellitus.

Assessing the exact level of influence of the HIV-infection as an independant factor and thus establishing equivalences with the non-infected population's risk models is challenging:

Some studies have considered the intima-media thickening of carotide arteries(higher specificity with internal carotide arteries) as an efficient marker of atherosclerotic evolution and thus as a CVD predicting factor. Comparing the intima-media thickening of the carotide arteries corelated with different factors could therefore mesure the relative influence of the HIV infection as an independant risk factor compared to the other traditional CVD risks factors. Comparisons in between HIV population and controls (after adjustment for demographic and traditional CVD risk factors) have revealed that HIV-infection induced intima-media thickening was similar to the effects associated with male gender, smoking status and diabetes mellitus [51]. These findings suggest that HIV infection can be considered as an independent risk factor for atherosclerosis similar to the level of risk associated with male gender, smoking status and diabetes.

Among the HIV-infected population in care in Croatia in 2015, a high number of patients need interventions to reduce their cardiovascular disease risks. About one fifth to more than one third of patients, depending on the risk equation used, need intensive lifestyle modifications (cessation of smoking, diet, or weight loss) and lipid lowering therapy.

Certain drugs used for HIV treatment, like lopinavir/ritonavir, indinavir/ ritonavir, amprenavir, and fosamprenavir have been associated with an increased risk for myocardial infarction [table 1]. Abacavir has also for long been correlated (controversially) with CVD. Guidelines recommend its cautious use in patients with a high CVD risks. However, in Croatia abacavir is frequently used due to the higher cost of tenofovir- based formulations compared to abacavir formulations.

Another study, also based on the previous four prediction models, assessed the prevalence of eligibility for lipid lowering therapy among a HIV-infected population extended to Serbia (Belgrade and Zagreb combined HIV-treated population, forming a larger sample, very similar to the Croatian subgroup though) [53].

The statins eligibility was assessed according to the 2013 American college of cardiology/American heart association (ACC/AHA) guidelines, the European AIDS Society Guidelines (EACS) and the European Atherosclerosis Society (ESC/EAS)

guidelines for CVD prevention in HIV infected patients on ART. On figure 16 we can notice a discrepancy between statins recommendations of the ACC/AHA (37.9%) and the EACS (21.3%) and ESC/EAS (25.6%), current lipid lowering therapies recommendations for eligibility should therefore be applied with caution in the HIV-infected population. But still, this prevalence of lipid-lowering indication is significantly high in all considered models!

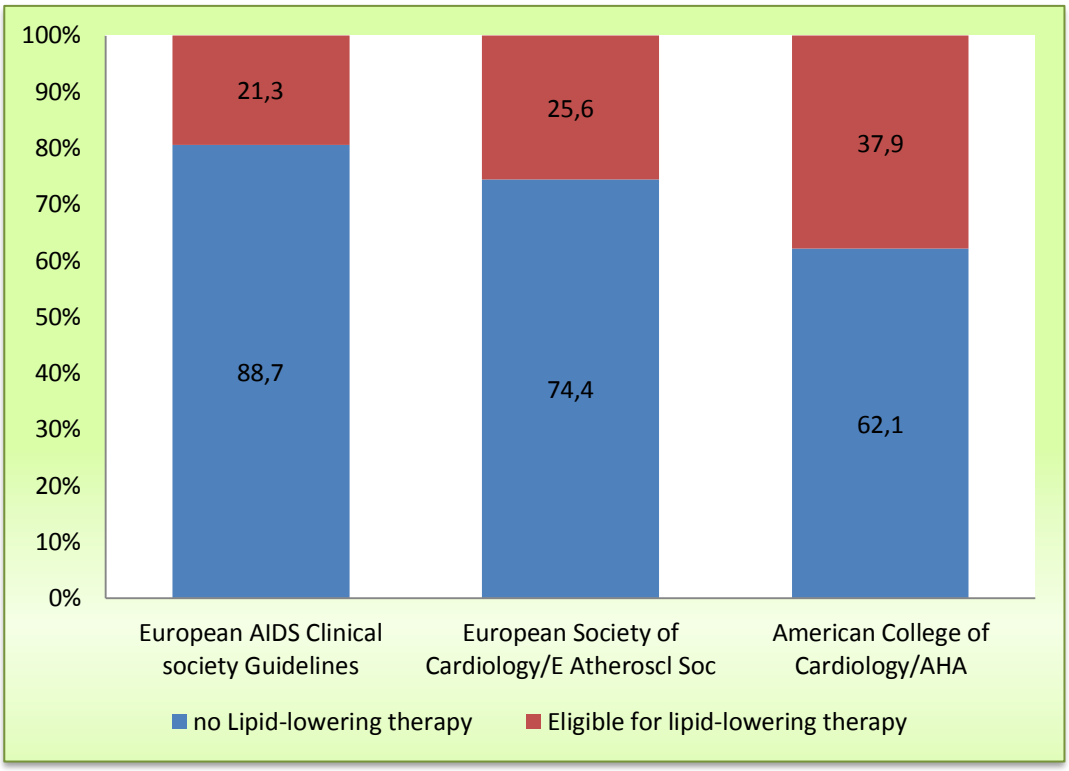


Figure 16: Prevalence of Lipid-lowering therapy eligibility.

Conclusion

The HIV-treated population of Croatia combines a constellation of significantly prevalent individual risk factors:

- **42% are current smokers!**
- **23% are hypertensive.**
- **34% have Hypercholesterolemia (>6.2 mmol/L).**
- **38% of patients are overweight.**
- **12% are obese.**

- **27% exhibit metabolic syndrome.**
- **7.8% of patients suffered past cardiovascular event.**
- **12.9% patients have a family history of premature cardiovascular event.**
- **21% of patients are already treated for high blood pressure.**
- **18.4% are already treated with lipid-lowering agents.**
- **46% of the studied population have an abacavir-including regimen.**
- **10% of patients have a detectable viral load.**
- **11.6% of patients have a low CD4+ cell count.**

The prevalence of compound major CVD risk factors is therefore high. All these factors synergetically interact as worthening the already cardiovascularly debilitating HIV infection per se. Preventing cardiovascular events in HIV-infected persons in Croatia should be a priority.

Management of "high-risk for CVD" HIV-infected patients

Antiretroviral treatment started on time

Because HIV replication per se directly damages the myocardium, and can worsen any CVD risk models score, the European Aids Clinical Society (EACS) recommends to initiate ART even before CD4+ cell count drops below 500 cells/μL.

Prevention of cardiovascular disease and lifestyle modification Cardiovascular risk in HIV patients needs to be evaluated before starting and 3 to 6 months after initiating a ART regimen. Of note, a careful selection of antiretroviral combination, (provided unlimited access to the least detrimental drugs regarding lipid and glucose metabolism) is of very first importance. Because cardiovascular risk management is necessary to counter balance the increased cardiovascular morbidity in this HIV-infected population, the interventions for cardiovascular risk reduction should follow those of the general population considered at "high risk of CVD" by any CVD

assessment models or the specific HIV-infected patients oriented CVD risk model like the DAD(R) model (see www.cphiv.dk/tools.aspx).

The modifiable risk factors should be aggressively handled towards maximum reduction: smoking status, high blood pressure, diabetes, excessive BMI, dyslipidemias; drug treatments being reserved for the subgroups where benefits are considered to outweigh potential harm.

Dyslipidemias management

Even though, the increased risk of CVD by HIV infection itself has yet to be reflected in conventional risk calculations, this increased risk is a valuable argument for lipid-lowering treatment in dyslipidemic HIV-infected patients even if this risk can be overestimated by conventional risk calculation [53]. Appropriate use of lipid-lowering drugs in these patients requires a thorough attention towards multiple drugs interactions between HIV therapies and commonly used cardiovascular drugs.

The problem with statin therapy in patients receiving antiretroviral therapy is not lack of efficacy in reducing LDL-C level, but drug interactions with PIs and NNRTIs. The PIs inhibit cytochrome P450 (CYP) 3A4 isoenzymes, which metabolize some statins: Drug interactions that raise statins level, leading to potential hepatotoxicity, myopathy and rhabdomyolysis are then of particular concern for HIV-infected patients. Simvastatin and lovastatin are metabolized by CYP 3A4, thus, simvastatin or lovastatin should not be used by PI treated patients. Atorvastatin is less extensively metabolized by CYP 3A4, so a carefully monitored use is possible. Pravastatin undergoes sulfurylation and then bypasses CYP450 isoenzymes catabolic pathway. However, combined with saquinavir/ritonavir, atorvastatin was increased almost 2-fold and pravastatin was decreased by half (simvastatin was increased more than 30-fold in this study)[54].So a cautious introduction of these two statins, atorvastatin and pravastatin is mandatory, no matter their relatively less sensible pharmacokinetic properties regarding CYP450 isoenzymes inhibitors.

Rosuvastatin is a very potent statin with a relatively lower potential for drug interactions. But some PIs increase rosuvastatin blood levels via a non-CYP3A4-related mechanism: Rosuvastatin maximum concentration was increased 4.7-fold by lopinavir/ritonavir [55] and 6-fold by atazanavir/ritonavir (most likely by increasing

rosuvastatin's oral bioavailability) [56]. Thus, high-dose rosuvastatin should be avoided by patients receiving these PIs. Interestingly no change in rosuvastatin concentration was observed with fosamprenavir/ritonavir [57].

In general, the potential for inhibition of statin metabolism is as follows: simvastatin and lovastatin > atorvastatin and rosuvastatin >> pravastatin.

Non-nucleoside reverse transcriptase inhibitors on the other hand are inducers of CYP 450 and can potentially reduce drug levels of drugs.
Efavirenz lowers simvastatin (and likely lovastatin) level by 60%, atorvastatin activity by 34%, and, paradoxically, pravastatin level by 40% (Pravastatin is cleared by the kidney so intuitively it shouldn't be influenced by drug interactions inhibiting CYP450 isoenzymes [57]. Higher levels of such statin drugs should be needed, but there is potential risk of "overdose" and would put patients at risk for rhabdomyolysis.
Delavirdine inhibits hepatic cytochrome P450 metabolism [54]. Thus, delavirdine increases statin levels and the risk of statin-related adverse effects similarly to PIs.

Modification of antiretroviral therapy

In HIV patients on ART who have had a newly developed a cardiovascular event or developed a substantial increase in cardiovascular risk, ART modification may represent an option to replace antiretroviral drugs with a risk of enhancing cardiovascular risk by more metabolic-friendly ones. Treatment modifications would include replacement of PI (especially ritonavir-boosted PI-based therapy) with non-nucleoside reverse transcriptase inhibitors (NNRTI), raltegravir or by another PI with less metabolic disturbances. Other modification could be to consider replacing stavudine, azidothymidine, or abacavir with tenofovir (see Table 1) or use a NRTI sparing regimen.
But a change in ART regimen in patients with an undetectable viral load and otherwise tolerating their current regimen well, shouldn't be an option for the only aim at preventing potential metabolic complications.

Niacin

In HIV-infected patients, niacin can decrease TG up to 32%, non HDL-cholesterol by 9% and up to 19% and increase HDL-cholesterol by 3% to 15% [58,59]. Because it can cause insulin resistance even in nondiabetic patients [58] niacin has been avoided as a first line therapy for patients using PIs, but studies in diabetic subjects suggest that this insulin resistance effect is only mild in control of glycaemia for these diabetic patients [61,62].

Fibrate

In HIV-infected patients, fibrates are not as potent as statins in preventing cardiovascular disease. Although less effective in lowering LDL-cholesterol, the ability of fibrates to increase HDL-cholesterol and to lower triglycerides levels justify their combined use with statins. Studies with HIV-1 patients treated with PI-based therapy and fibrates, including gemfibrozil, bezafibrate or fenofibrate, showed a significant reduction in the concentration of TC, TG and hypertriglyceridemia [63-65]. Fibrates appear as a suitable alternative for the treatment of dyslipidemia associated with HIV, especially in the presence of hypertriglyceridemia. The association between fibrates and statins has been used with relative safety in the general population except for the combination of statins and gemfibrozil (gemfibrozil is a potent CYP450 system inhibitor), which is not recommended [65-67]. The association has shown positive results in HIV-associated dyslipidemia, particularly for the pravastatin/fenofibrate combination which appeared safe and has promoted a significant improvement in lipid parameters [68,69]. However, Periodic monitoring of serum creatinine, creatine kinase, and transaminases should be performed for the use of fibrates [64,65,67].

Fish oil

Liver cod oil and other fish oils containing eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) [omega-3 fatty acids] have strong anti-inflammatory and anti-platelets properties [70,71]. They restore the ratio omega-3/omega-6; ideally around 1:5 but unfortunately more often around 1:20 in the nowadays occidental (inappropriate) diet … The rapid evolution of human diet away from a 1:5 omega-3

over omega-6 ratio, such as during the pre-intensive agriculture era has been too fast for human metabolism to adapte to such rapid changes [72]. This is commonly believed to be the reason why modern diets are correlated with many inflammatory disorders. It is now understood that inflammation is a major component in the pathogenesis of atherosclerosis [73]. Consumption of omega-3 fatty acids from marine sources lowers markers of inflammation in the blood such as C-reactive protein, interleukin 6, and TNF alpha [74]. HIV-infected patients consuming fish oil supplements have efficiently reduced their triglycerides levels [71] and associated with fenofibrate, the results on TG are additive.

Extra virgin olive oil

Even if extra virgin olive oil's fatty acids profile is quite neutral over the omega-3/omega-6 ratio, it contains a phenolic fraction that subsides inflammation. A randomized, crossover, controlled trial including 39 HIV-positive male participants using ART, has been able to show that extra virgin olive oil (compared to refined olive oil) lowers high-sensitivity C-reactive protein[75]. Other inflammatory and biological markers were monitored (interleukin-6, fibrinogen, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, malondialdehyde, glutathione-peroxidase, superoxide dismutase, oxidized LDL and von Willebrand factor) but extra virgin olive oil only lowered erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hsCRP). Anyway, in participants using lopinavir/ritonavir, ESR and hsCRP concentrations decreased 62% and 151%, respectively, after extra virgin olive oil administration suggesting that such a supplementation could be beneficial to hinder inflammatory and oxidative subclinical processes always present in HIV-infection. Even successfully treated HIV-infected patients may still have an increased cardiovascular risk, which might be related to inflammation and dyslipidemia induced by HIV and/or antiretroviral therapy. A study suggests that in patients with undetectable viral load, there is a significant association between markers of inflammation and serum levels of cholesterol and triglycerides as well as the cholesterol/HDL-cholesterol ratio [76].

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Biography

Born on the atlantic coast of France where he spent his educational years till his graduation in Master of clinical psychology, the author has then had the opportunity to complete his medical education at the medical university of Zagreb.